Case Report

Multicentric Reticulohistiocytosis Responding to Tumor Necrosis Factor-α Inhibition in a Renal Transplant Patient

SEAN E. SHANNON, H. RALPH SCHUMACHER, SALLY SELF, and ALAN N. BROWN

ABSTRACT. Multicentric reticulohistiocytosis (MRH) is a rare systemic disease that characteristically produces severe erosive arthritis of the distal and proximal interphalangeal joints along with cutaneous nodules over the upper extremities and face, but it can be found in other organs. There is no known etiology, and it often remits spontaneously within 5–10 years, but can result in severe disfigurement. The diagnosis is made when histologic analysis of involved synovium or cutaneous nodules reveals characteristic histopathology. We describe a case of MRH manifesting as erosive arthritis that developed despite immunosuppressive therapy. Based on studies reporting tumor necrosis factor-α (TNF-α) positive cells within MRH lesions, we began treatment with TNF-α inhibition. Within 2 months the patient showed dramatic clinical and serologic improvement that was maintained until she stopped treatment secondary to an upper respiratory tract infection. Once treatment was restarted, the symptoms again improved. (J Rheumatol 2005;32:565–7)

Key Indexing Terms:
HISTIOCYTOSIS NON-LANGERHANS CELL IMMUNOSUPPRESSIVE AGENTS
KIDNEY TRANSPLANT RECEPTORS TUMOR NECROSIS FACTOR

Multicentric reticulohistiocytosis (MRH) is a rare systemic disease that characteristically produces severe erosive arthritis of the distal (DIP) and proximal interphalangeal (PIP) joints along with cutaneous nodules over the upper extremities and face, but it can be found in almost any organ[1]. There is no known etiology and it often remits spontaneously within 5–10 years, but can result in severe disfigurement[2]. The diagnosis is made when histologic analysis of involved synovium or cutaneous nodules reveals characteristic histopathology.

We describe a case of MRH manifesting as erosive arthritis that developed despite immunosuppressive therapy. Based on studies reporting tumor necrosis factor-α (TNF-α) positive cells within MRH lesions, we began treatment with TNF-α inhibition. Within 2 months the patient showed dramatic clinical and serologic improvement that was maintained until she stopped treatment secondary to an upper respiratory tract infection. Once treatment was restarted, the symptoms again improved.

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CASE REPORT

A 37-year-old African American woman presented with a 4-month history of symmetric swelling in her DIP joints and pain in her right thumb. Since returning to college in the fall of 2002, she noticed a progressive laxity and swelling of her DIP joints making picking up small objects difficult. She had been given corticosteroid therapy at the age of 2 for primary segmental glomerulosclerosis and as her renal function declined immunosuppressive therapy was incrementally increased. At the age of 28, cyclosporine was added; mycophenolate mofetil was added at the age of 35 following a renal transplant. Other history included a greater than 5-year history of Raynaud's phenomenon, hypercholesterolemia, and a 1.1 cm lung nodule determined to be benign after 3 years of close radiographic monitoring. She was up to date on routine gynecologic screening. Family history was significant for a sister with systemic lupus erythematosus. There was no travel history, no pets, no illicit drug use, or known toxin exposure. Upon presentation, she was taking mycophenolate mofetil 250 mg bid, cyclosporine 125 mg bid, prednisone 10 mg qd, and simvastatin 40 mg qd, and had recently started tramadol 50 mg tid.

Examination was remarkable for fine flesh colored nodules clustered in the perioral region and over the forehead. Musculoskeletal examination revealed large painful boggy DIP joints that were unstable on examination without warmth or erythema (Figure 1). The remainder of the examination was unremarkable, and nailfold capillaroscopy was normal. The right first interphalangeal (IP) joint was aspirated and revealed many white blood cells under light microscopy, and no crystals were seen under polarized microscopy.

Laboratory studies revealed a normocytic anemia [H/H 10.2 (12.0–16.0)/32.4 (37.0–47.0), mean corpuscular volume 93.0 fl (81.0–99.0)] with normal platelet and white blood cell count, and elevated

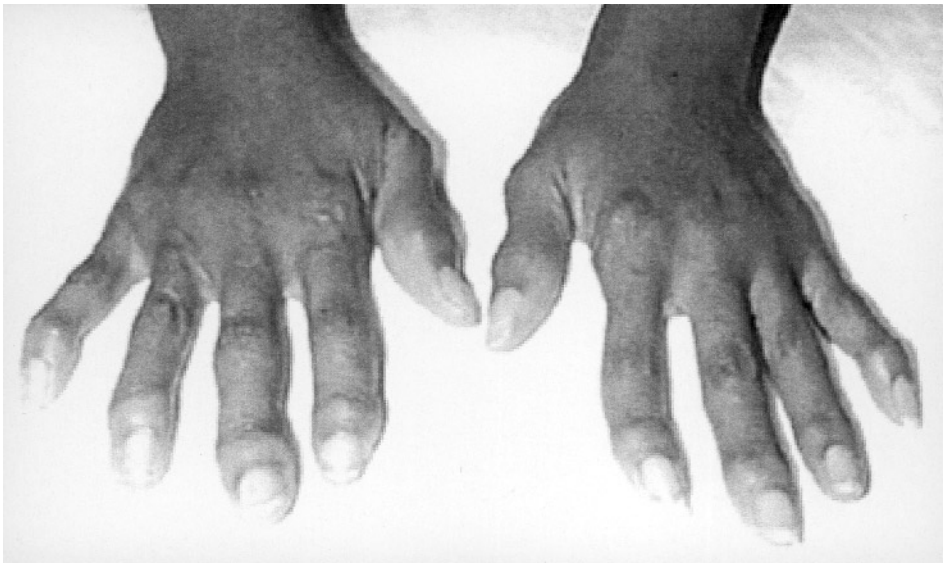

Figure 1. Musculoskeletal examination revealed large painful boggy DIP joints that were unstable on examination without warmth or erythema.

sedimentation rate (ESR, > 100 mm/h) and C-reactive protein [CRP, 33 mg/dl (0.0–0.74)]. Antinuclear antibodies and rheumatoid factor were both negative; serum electrolytes were within normal limits. A purified protein derivative test was negative at 48 h.

Radiography of the hands revealed symmetric erosion of the DIP and first IP joints (Figure 2).

A synovial tissue sample from the right IP joint was obtained. Under light microscopy, mild hyperplasia of the synovial cells was noted with scattered monocytes and occasional giant cells (Figure 3). Immunohistochemical staining identified the infiltrating cells to be populated by mature T lymphocytes, monocytes, and macrophages (CD 68+, CD 3+, and CD 45+). CD 1, S 100, and CD 30 were not present, indicating the cells were not dendritic, Langerhans cells, or lymphocytic-histocytic cells.

Facial nodules were evaluated by a dermatologist and found to be consistent with milia; they were not biopsied.

The diagnosis of MRH was made and adalimumab 40 mg administered subcutaneously every other week was added to her medical regimen. Eight weeks later she improved significantly and was no longer taking nonsteroidal antiinflammatory drugs; the CRP normalized at 0.09 mg/dl and the ESR decreased to 39 mm/h. After 4 months of therapy the ESR had normalized at 19 mm/h and CRP remained normal. Five months into therapy she developed a sinus infection that was treated with antibiotics, and adalimumab was withheld for one month. She returned to clinic 2 days after restarting therapy and was found to have synovitis in all DIP and PIP joints. Her ESR remained normal (9 mm/h), but the CRP was elevated at 1.34 mg/dl. Two months later, she had no evidence of synovitis and her CRP had normalized at 0.19 mg/dl.

DISCUSSION

MRH most commonly presents as arthritis and cutaneous

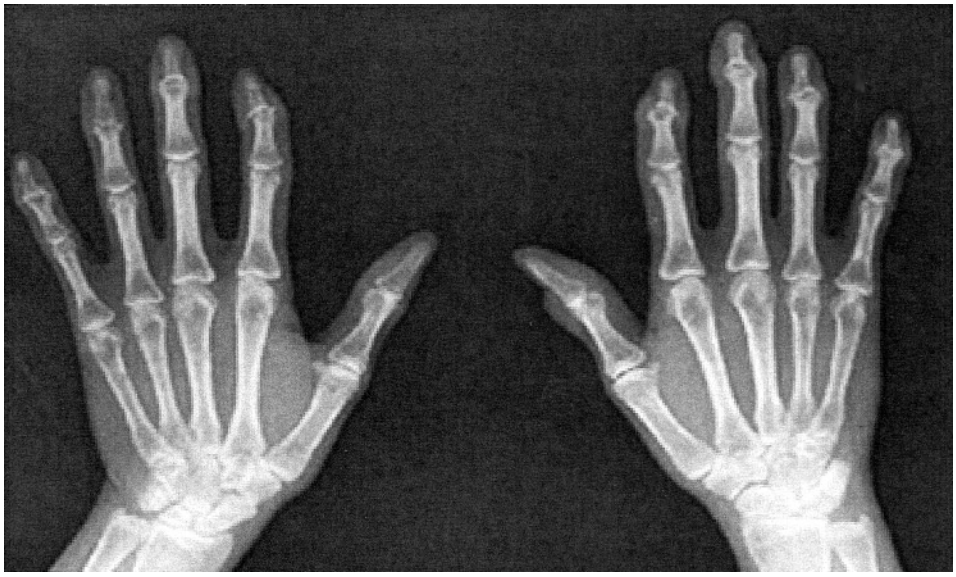

Figure 2. Radiography of the hands revealed symmetric erosion of the DIP and first IP joints.

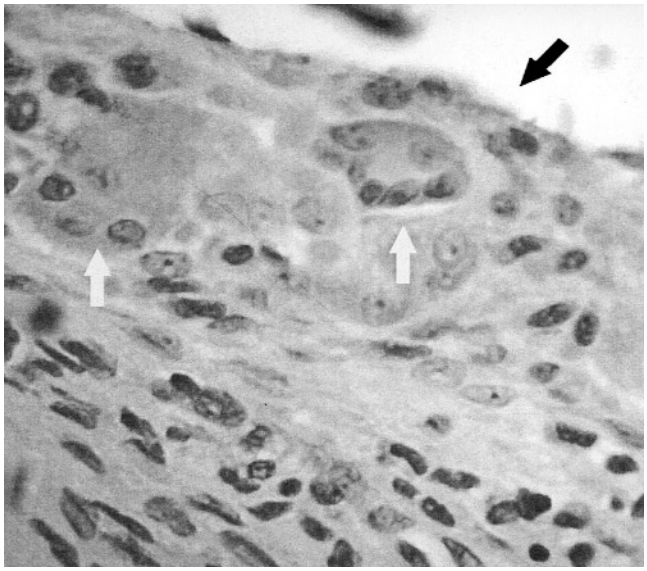

Figure 3. Hematoxylin-eosin staining of the synovial biopsy showing multinucleate giant cells (white arrows) and mixed inflammatory cells within the synovial membrane. The synovial surface is indicated by the black arrow.

nodules, but it can affect any organ[1]. The arthritis associated with MRH is erosive, symmetric, and polyarticular, and predominantly affects the peripheral joints. The most common extraarticular manifestation is a reddish-brown papulonodular eruption over the face, digits, and extensor surfaces of the upper extremities[1]. Cutaneous involvement occurs first in 18% of patients, and develops simultaneously with arthritis in 21%, while the remaining cases present with arthritis alone, developing skin lesions an average of 3 years after arthritis[3]. Biopsies from all involved tissues reveal characteristic giant cells whose cellular origin has been extensively investigated. A review by Gorman, *et al* found that reported immunohistochemical findings were variable, and some studies suggested a dermal dendrocyte[4] or lymphocyte[5,6] origin, but concluded that the majority of evidence supports a monocyte/macrophage origin[7-9]. Two studies reported increased levels of TNF-α in MRH[10,11]. Matejicka, *et al* reported a case of MRH that was unresponsive to multiple disease modifying agents, but 6 weeks after starting therapy with etanercept the patient showed marked improvement[11].

Our study is a unique case of MRH that developed despite aggressive immunosuppression, but improved rapidly with the addition of TNF-α inhibition, supporting the findings of Matejicka, *et al*[12]. There are case reports of MRH responding to corticosteroid and various immunosuppressive (or cytotoxic) agents[13]. Our patient's synovial histopathology lacked the abundance of multinucleated giant cells seen in previous cases of MRH, but we feel this is explained by her previous immunosuppressive therapy. When adalimumab was withheld, our patient's symptoms not only returned but progressed to involve the PIP joints; however, the symptoms were quickly controlled by restarting therapy, suggesting that TNF-α inhibition rapidly suppresses the underlying pathology of MRH and therefore may be able to suppress the erosive changes seen in MRH.

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